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09/581,500	11/14/2000	Christine Van Broeckhoven	B0192/7019	9967

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EXAMINER	
MYERS, CARLA J	

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1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/581,500	VAN BROECKHOVEN ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the amendment filed October 20, 2005 . Applicant's arguments have been fully considered but are not persuasive to overcome all grounds of rejection. All rejections not reiterated herein are hereby withdrawn. This action is made final.

Claims 1-5 are pending. All rejections not reiterated herein are hereby withdrawn. This action is made final.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Breadth of the Claims:

The claims are drawn to method for identifying a human coding region/gene ,including mutated and polymorphic variants thereof, which are associated with a bipolar disorder, comprising identifying the position of a coding region or gene between the markers D18S68 and D18S979 that can be compared to an "equivalent region" in a person afflicted with a mood disorder or a related disorder, and detecting differences in the coding region or gene of said individual wherein a difference in the coding region or gene or an equivalent region identifies a coding region or gene or mutated or polymorphic variant associated with the mood disorder or related disorder. The claims encompass identifying coding regions, genes, mutations and polymorphisms associated with bipolar I or bipolar II type disorders. The claims as broadly written encompass methods of searching for known or unknown coding regions and genes and for mutations and polymorphisms in the 9.8cM region between the markers D18S68 and D18S979 and trying to establish a correlation between these regions/genes, mutations and polymorphisms and the occurrence of any mood disorder or related disorder. Additionally, the claims encompass detecting differences in the region between D18S68-D18S979 or D18S60-D18S61 and "equivalent regions" of an individual afflicted with a disorder. The specification does not specifically define what is encompassed by "equivalent regions." Accordingly, such regions have been interpreted as encompassing regions having some unstated degree of similar sequence and similar location in the genome as the regions flanked by the D18S68-D18S979 or D18S60-D18S61 markers.

Nature of the Invention

The claims encompass methods for detecting a coding region or gene by assaying for the presence of genetic variation between markers D18S68 and D18S979. The invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

Teachings in the Specification and State of the Art:

The specification teaches that a susceptibility locus for bipolar disease had been previously identified within the region of 18q21-q23 (page 4). The specification (page 24-25) provides the results of a study from a Belgian family (MAD31) having a BPII proband wherein the susceptibility locus was refined to include a region of 8.9 cM located between the 18q markers D18S68 to D18S979. It is stated that this region may now be "used to locate, isolate and sequence a gene or genes which influences psychiatric health and mood" (page 5). Further, "once candidate genes have been identified it is possible to assess the susceptibility of an individual to a mood disorder or related disorder by detecting the presence of a polymorphism associated with the mood disorder or related disorder in such genes."

The specification teaches multi-linkage analysis of STRs located between the markers of D18S51 and D18S61 for cosegregation with bipolar II disease in family MAD31. The results of LOD score analysis is set forth in Table 2 (page 31). The highest individual LOD score obtained for any marker was 2.01. However, as set forth on page

4 of the specification, "A LOD score of 3 (or likelihood ratio of 1000 or greater) is taken as significant statistical evidence for linkage."

The specification does not disclose a single gene or coding region within the region of D18S68-D18S979. Further, the specification does not disclose any particular mutations or polymorphisms within the region of D18S68-D18S979 which are associated with BP II. Moreover, the specification does not provide any results regarding the linkage of the D18S68-D18S979 markers or other markers within this region and the occurrence of other bipolar disorders.

The Predictability or Unpredictability of the Art and Degree of Experimentation:

The art of identifying genes associated with a disease and detecting the presence of novel mutations associated with the occurrence of disease is highly unpredictable. Once a region associated with a gene is known, extensive experimentation remains to determine which, if any, genes within this region are sufficiently linked to a disease in order to allow for diagnosis of the disease by detecting the gene. Further, once a gene associated with a disease is identified, significant experimentation is also required to identify particular mutations and polymorphisms within that gene which are diagnostic of disease. The identity of the gene/coding region and the identity of the mutations and polymorphisms are the novel features required to practice the claimed invention. However, the specification does not teach the structural and functional properties of the coding regions/genes or mutations/polymorphisms. Rather, the specification outlines the methodology by which a researcher could perform extensive, trial-by-error experimentation in order to try to identify genes/coding regions

and mutations/polymorphisms which could be used within the claimed methods. Disclosure of a 8.9 cM region linked to BPII is not equivalent to disclosing specific genes/coding regions and nucleotide variations which are associated with BP or other mood related disorders. To identify genes or mutations within this 8.9 cM region requires significant experimentation in which researchers may be required to create a clonal library containing candidate cDNAs which would then be sequenced and compared to nucleic acid databases to identify a gene or genes which may constitute the bipolar susceptibility gene. The cDNAs identified that map to the minimal candidate region would then used as probes to screen a contig library. This screening then identifies new markers which are used to genotype the linkage disequilibrium sample. The cDNAs identified by these screens are then used to screen patient DNA for mutations and polymorphisms associated with bipolar disorders. Such random, trial-by-error experimentation is considered to be undue.

The art corroborates the unpredictability in identifying polymorphisms and mutations associated with BP and in identifying a specific loci within chromosome 18 that is definitively associated with BP. For example, McInnes (Proceedings of the National Academies of Sciences, USA. November 1996. 93: 13060-13065) teaches that interpreting results form linkage analysis of bipolar mood disorder and other behavioral phenotypes is very difficult and often misleading because behavioral phenotypes are difficult to define, as they are etiologically heterogeneous and there is a lack of knowledge as to the mode of transmission of these diseases. McInnes concluded that it is unlikely that any one linkage study will yield sufficient evidence to localize a gene for

any psychiatric disorder (page 13060, col. 2, paragraph 1). McInnes performed a genome screening analysis for possible genes associated with BP and found suggestive lod scores in segments 18q, 18p and 11p. McInnes teaches that genome screening is the first step of a multi-step process for identifying genes for complex traits and that several additional steps and experiments would be required to delineate a clear candidate region (page 13064, col. 2). Gerson (Neuropsychopharmacology. 1998. 18: 232-242) reviewed the progress in identifying genes associated with manic-depressive illness and concluded that while chromosome 18, and particularly the short arm of chromosome 18, is one of the best candidate locations for a bipolar susceptibility gene, and that the positive linkage results represent important progress, scientists are still a long way from demonstrating a disease mutation correlated with bipolar illness (page 239, col. 2). Nothen (Molecular Psychiatry. 1999. 4: 76-84) concluded that as late as 1999 that the data in the art supports the hypothesis that a susceptibility locus exists and may specifically exist on chromosome 18, but does not provide a reasonable expectation that polymorphisms in the region of 18q are associated with a bipolar susceptibility locus or what that locus will be. Nothen (page 82) states that "(a)ny single study will be insufficient to provide convincing proof for a susceptibility locus in a complex disease because of unknown mode of inheritance, genetic heterogeneity, and nongenetic factors."

The teachings of Lucentini (The Scientist. December 2004, page 20) further highlight the unpredictability in the art of establishing an association between a mutation/polymorphism and the occurrence of a disease or condition. As discussed by

Lucentini, reproducible association studies are "few and far between." The reference reports that "when a finding is first published linking a given gene with a complex disease, there is only roughly a one third chance that studies will reliably confirm the finding. When they do, they usually find the link is weaker than initially estimated. The first finding is usually 'spurious, or it is true, but it happens to be really exaggerated, ' ...there may be no way to predict which new gene-association studies will be verified with multiple replication."

The teachings of Goossens et al (European Journal of Human Genetics, 2000; of which 2 of the present inventors are co-authors) also supports the unpredictability in the art. In this post-filing date reference, the authors report that no association was found between triplet repeats in the 18q21.33-q23 region and bipolar disease family MAD31 and 75 unrelated BP cases (see page 388). With particular respect to claims 7, 9,10, 20, 26 and 27, the specification and prior art do not teach any particular trinucleotide repeats in the regions between D18S60-18S61 or D18S68-D18S979 whose presence is indicative of a coding region or gene or mutated or polymorphic variants thereof associated with mood disorders or related disorders.

Further, it is highly unpredictable as to whether the linkage results obtained with family MAD31 would be applicable to other bipolar disorders. The different types of bipolar disorders are believed to be genetically distinct. These disorders also have different symptomologies. No evidence or scientific arguments have been presented to establish that the results obtained with one family having a BPII proband can be extrapolated to all other types of bipolar disorders.

Amount of Direction or Guidance Provided by the Specification:

The specification does not provide any specific guidance as to how to predictably identify a coding region / gene or mutation / polymorphism in the D18S68-D18S979 region which is associated with and can be used to diagnose a mood disorder or a related disorder. While methods for performing linkage analysis and for sequencing genes and comparing the sequence of genes from patients and control individuals are known in the art, such methods provide only the general guidelines that allow researchers to search for novel genes and mutations. Providing methods for searching for a gene or mutation is not equivalent to teaching specific genes and mutations associated with mood disorders and related disorders. Even by following the method steps set forth in the present claims, one would not arrive at coding regions/genes or variants thereof that are associated with mood disorders. The mere presence of a genetic variation between the DNA of one affected person and the DNA of one control person does not alone indicate that the variation is associated with a disorder, since many of the variants will not be specific to the affected individuals. That is, the variants are equally likely to represent polymorphisms present in the general population and not specifically associated with a mood disorder in the general population.

The teachings in the specification do not provide a reasonable expectation that one of skill in the art can identify variants associated with bipolar mood disorder or can identify a bipolar susceptibility locus without undue experimentation because of the high level of unpredictability in the art (as discussed above) and because the specification has not provided evidence that would allow the skilled artisan to predict the location and

identity of specific bipolar susceptibility genes and mutations / polymorphisms. The specification presents data defining a smaller region of the 18q arm which has a higher probability of containing a susceptibility locus, but as of 1999, the art indicates that scientists are a long way from pinpointing specific genes, polymorphisms and mutations that are associated with bipolar disease or related disorders. The specification describes a research project for searching for genes and mutations that may exist in the defined region but the protocol described constitutes undue experimentation because the skilled artisan would be required to perform a large amount of essentially random screening of the defined region and would not be able to reasonably predict from the specification the identity of the gene or mutations associated with BP. Furthermore, the claims as written are directed to a research project without a predictable outcome because they encompass methods which detect novel bipolar disease susceptibility genes and polymorphisms. The art makes clear that this objective is of great interest and the target of extensive research by many groups. In fact, many groups have taken the same approach as described in the specification for identifying such a bipolar locus without success. The specification essentially suggests that the artisan should analyze all possible mutations or polymorphisms within the 8.9 million bp region of D18S to D18S979 and then determine which variations within this region represent mutations or polymorphisms that could be used to diagnose a mood disorder. Such experimentation is considered to be undue.

Working Examples:

The specification does not provide any working examples of methods in which a coding region / gene or mutated or polymorphic variant thereof is identified and wherein the coding region / gene or variant is associated with mood disorder or any other related disorder.

Conclusions:

Case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that "(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement". In the instant case, the claims do not bear a reasonable correlation to the scope of enablement because the specification does not teach a single coding region or gene or variant thereof which is associated with a bipolar disorder. The specification does not provide the novel aspects of the claimed invention because the disclosure of a 8.9 cM region linked to BPII is not equivalent to teaching specific sequences that constitute coding regions / genes or mutations that are associated with a BP disorder. The specification provides the researcher with only

an invitation to experiment and to try to find a new gene or mutation that is associated with mood disorder and which could be used to diagnose a bipolar disorder. No specific guidance is provided as to what would be the identity of such a gene or mutation / polymorphism. Accordingly, given the high level of unpredictability in the art and the lack of specific guidance provide in the specification and prior art, it would require undue experimentation for one of skill in the art to practice the claimed invention.

RESPONSE TO ARGUMENTS:

Applicants arguments and the 132 Declaration of Christine Van Broeckhoven have been fully considered but are not persuasive to overcome the present grounds of rejection.

It is first noted that the claims are drawn to methods for identifying a gene or coding region, or a mutated or polymorphic variant thereof, which is associated with a bipolar disorder. The identification of such a gene, mutation or polymorphism is accomplished by comparing a sequencing within the 8.9 cM region D18S68 to D18S979 or the region D18S60-D18S61 of a person afflicted with a bipolar disorder to an equivalent region of human DNA (the source of which is undefined). The presence of any sequence difference within these regions is interpreted as indicating the presence of a coding region or gene or a mutation or a polymorphism that is associated with a bipolar disorder. However, those of skill in the art would not interpret the results obtained by comparing one afflicted individual's DNA to an unstated source of DNA as indicating the presence of a gene, coding region, mutation or polymorphism associated with bipolar disorder. The comparison of the DNA sequences between one individual

with bipolar disorder to the DNA sequences of another sample would not provide meaningful results that would allow one to draw a conclusion that the identified sequence difference was associated with bipolar disorder since the identification of a mutation or polymorphism associated with a disorder can only be ascertained by determining that the mutation or polymorphism is present in a statistically significant number of afflicted individuals and that the mutation or polymorphism is absent in normal, control individuals which are representative of the general population. Polymorphisms occur throughout the human genome at a frequency of one out of about every 100 to 300 bases. Those of skill in the art would recognized that not all polymorphisms present between D18S68 to D18S979 will be linked to bipolar disease. Thereby, it is clear that the sequence comparison step alone does not identify a mutation or polymorphism associated with bipolar disorder. The identity of a polymorphism which would be linked to bipolar disorders can only be ascertained through extensive trial-by-error experimentation. The claims as written set forth the first steps of a research project. The results of this research project do not in fact identify a gene, mutation or polymorphism associated with bipolar disorder. Rather, the identification of a difference in the sequences provides a starting point for researchers to begin investigating the sequence difference to determine its association with a bipolar disorder. Further, detecting a difference in the sequence between D18S69 to D18S979 identifies only a difference in the nucleotide sequence. The identification of a nucleotide difference is not equivalent to the identification of a gene or coding region. The identification of a gene or coding region can only be accomplished by extensive

experimentation, which includes sequencing portions of this region and searching for an open reading frame and for regulatory sequences associated with the ORF. As set forth in *Brenner v. Manson,* 383 US 519, 535-536, 148 USPQ 689, 696 (1966), "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion." In the present situation, Applicants have not identified a single coding region or gene or a single mutation or polymorphism associated with bipolar disorder. Applicants have identified a narrower region of the human genome which might include a gene, mutation or polymorphism associated with bipolar disorder. However, the specification does not provide the novel aspects of the claimed invention – i.e., the identity of the nucleotides that constitute the gene, mutation or polymorphism. Rather, the specification provides only an invitation to researchers so that they may go out and seek the novel aspects of the claimed invention – i.e., an invitation to try to identify a gene, coding region, mutation or polymorphism associated with bipolar disorder.

In the response, Applicants traversed the rejection by arguing that the LOD score need not be greater than 3 because Applicants did not perform a complete genome scan of family MAD31, but rather a fragment of chromosome 18 was scanned using STR markers in a multilocus linkage analysis. Further, Applicants filed a 132 Declaration stating that "the lod score of +2.0 was indicative of significant linkage in this study, taking into account the design of the particular study carried out in family MAD31." The declaration points to page 245 of the Lander reference as teaching that for an interval of 20 cM a p value of 0.01 is "suggested for declaring confirmation of

linkage at the 5% level." However, the cited statement was made with respect to replication studies, wherein it is further stated that "Linkage results must be replicated to be credible. We suggest that the term 'replication study' should be reserved for situations in which *significant* linkage has already been obtained in an initial study (or combination of studies)....Because replication involves testing an established prior hypothesis, the multiple testing problem associated with genome-wide search does not apply." The results set forth in the present application do not appear to constitute a replication study. The 132 Declaration states that "Generally there is no need to state both the lod score and the P value for a given linkage study." This statement is true. However, it is noted that the Office action did not require that Applicants provide a p value for the study. Applicants state that "in the MAD 31 linkage study a lod score of 2.0 corresponds to a P value of 0.01 which according to the criteria of Lander and Kruglyak is sufficient for declaring confirmation of linkage at the 5% level." However, the response and declaration do not clarify how this p value was obtained – i.e., the basis for concluding that the lod score of 2.0 is equivalent to a p value of 0.01. Additionally, the disclosure of a lod score of 2.01 for 3 markers in the stated region (in "Model 1") does not provide sufficient evidence or guidance for obtaining, without undue experimentation, a gene, coding region, mutation or polymorphism in the region flanked by D18S68 to D18S979 or D18S60-D18S61. Further, it is noted that for "Model 1" the other markers in this region did not have lod scores that would be viewed as significant: the lod score for D18S68 and D18S346 was –0.19; the lod score for D18S969 was 1.40; the lod score for D18S979 was –0.18; the lod score for D18S61 was –0.21.

The response further traverses the rejection by arguing that the cited art does not establish that undue experimentation would be required to practice the claimed invention. Applicants assert that they have advanced the art by identifying a more specific and defined candidate region than the one previously available. However, narrowing the region to only 8.9 cM does not provide a more definitive and specific characterization of a gene, mutation or polymorphism that is associated with bipolar disease. The disclosure of a narrower region, while limiting to some extent the amount of research that must be must be done, does not in fact remove the unpredictability associated with identifying a new gene, mutation or polymorphism correlated. Again, there is no disclosure in the specification of a gene, mutation or polymorphism associated with bipolar disorder. The specification provides only the steps of the research project which one could practice in the hope of eventually identifying a gene, mutation or polymorphism associated with bipolar disorder. The fact that the region now consists of 8.9 cM, rather than the larger previously defined region of 18q21-q23, does not ensure a reasonable expectation of success that a gene, mutation or polymorphism associated with a bipolar disorder can be identified without undue experimentation.

Applicants argue that the teaching of Goossens is not relevant to the present invention because Goossens investigated specific trinucleotide repeats, i.e.. CAG/CTG repeats, to determine if the repeats were associated with bipolar disorder. It is argued that the results of Goossens do not preclude the possibility that other repeats in the region are associated with or causative of bipolar disorder. This argument has been fully considered but is not persuasive. It is first noted that claims 7, 9 , 10, 20, 26 and 27,

drawn to methods in which the detection of any triplet between D18S69-D18S979 is detected as indicative of the presence of a coding region or gene variant thereof associated with a mood disorder, were cancelled in the response. However, the teachings of Goossens are in fact relevant to the claimed invention. Goossens' results establish the unpredictability of identifying a marker in the D18S69-D18S979 region that is associated with bipolar since Goossens teaches that the CAG and GTG triplets between D18S69-D18S979 are not involved in BP disorder. The results emphasize that only through trial-by-error experimentation can one identify a repeat that is associated with bipolar. That is, knowledge that a region is linked to bipolar disorder does not allow one to immediately envision or obtain without undue experimentation, repeats (mutations or polymorphisms or other markers) that are associated with bipolar disorder.

Applicants state that "Nothen et al do not dispute that a bipolar susceptibility locus exists on chromosome 18, they merely conclude that it may be difficult to precisely locate the locus through further linkage studies." Applicants assert that there is no need to perform additional linkage studies because they have further defined the candidate region. However, while Applicants have further defined the candidate region, Applicants have not identified a gene, coding region, mutation or polymorphism that is correlated with bipolar disorder.

Applicants go on to cite WO 02/101044 (Del-Favero et al.) as teaching methods for trying to obtain a gene associated with bipolar using the same experimental procedures set forth in the present application. It is stated that the authors identified a

potential candidate gene, NCAG1, using these experimental procedures. Applicants admit that Del-Favero determined that "(n)o alleles, genotypes or haplotypes were found to be significantly associated with bipolar disorder, indicating that NCAG1 itself is not a candidate bipolar gene." Nonetheless, Applicants assert that the teachings of Del-Favero et al confirm the validity of the experimental approach. Applicants arguments and the teachings of Del-Favero et al have been fully considered. However, the cited reference does not establish the predictability of using the disclosed method to identify a gene or mutation associated with bipolar disorder. Rather, the cited reference actually emphasizes the unpredictability associated with identifying a novel gene or mutation linked with a disorder. As set forth by Del-Favero et al, even after a region has been identified that is linked to bipolar disorder and even with knowledge of the experimental techniques (which were known in the art prior to Applicants application), the ability to identify a gene or mutation linked with bipolar disorder remains unpredictable. Applicants state that the technique could identify a true candidate gene and assert that "(t)he experimental approach would be the same – only the result would be different." However, the specification as originally filed does not clearly describe the "result" or provide any evidence that applicants have obtained the desired "result" – i.e., does not define the gene, mutation or polymorphism in terms of its identity or specific location with the D18S68 to D18S979 region.

Applicants cite WO 03/02522 as teaching that a CAP2 gene and a polymorphism in this gene were identified using techniques similar to those taught in the present application. It is first noted that the inventors of this reference are co-inventors of the

present application. Thereby, Applicants are citing work, having a filing date at least 4 years after the present invention, as a means of trying to establish that those of skill in the art could follow the disclosed techniques to obtain a gene or mutation or polymorphism associated with BP. However, while the techniques used in the present invention may eventually allow other researchers to obtain, through extensive experimentation, a gene or polymorphism associated with bipolar disorder, the findings of the WO 03/02522 document do not indicate that the present invention enabled researchers to obtain such a gene by routine experimentation.

Applicants cite Cox and Bell as providing confirmation that the techniques used by the present inventors were known as early as 1989. However, what was not known in 1989 or at the time the invention was made, was the identity of a gene, mutation or polymorphism associated with bipolar disorder. Applicants state that the "difference between success and failure in identifying a particular coding region as a 'susceptibility gene' associated with a particular disease is purely a matter of statistics in the association study. Applicants submit that would not be considered to be 'random experimentation'. " However, Applicants interpretation of what constitutes routine experimentation is clearly in great contrast to what those of skill in the art view as "routine experimentation." It is maintained that it is not simply a matter of routine experimentation to identify a novel gene or mutation or polymorphism associated with bipolar disease. The extensive amount of experimentation that is discussed in the cited references provides evidence of this fact. Applicants cannot rely on the findings obtained 4 years after the filing of their application to enable the present invention.

There is no disclosure in the present specification of a CAP2 gene or of a polymorphism in CAP2 which is correlated with bipolar disorder. Further, the present application does not provide the specific guidance to lead one to the particular CAP2 gene or polymorphism in this gene. It is also noted that the WO 03/025222 reference also establishes the unpredictability of the claimed invention in that this reference teaches that there was not a significant difference between BP patients and controls in allele frequencies or genotype distribution for 5 of the identified SNPs (page 26). Also, while the T allele of the 942C>T polymorphism occurred at a higher frequency in male BP patients versus controls, "(i)n females no difference in allele or genotype distribution was observed between cases and controls" (page 27). The disclosure in the present application of general techniques for identifying polymorphisms does not lead one to the specific 942T polymorphism or to the finding that this polymorphism is associated with BP only in males. The specification and claims do not provide any specific guidance as to how to ascertain aprior which mutations/polymorphisms will be associated with BP only in male versus female patients.

The amount of guidance needed to enable the invention is related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Predictability or lack thereof in the art refers tot eh ability of one of skill in the art to extrapolate the disclosed or known results to the invention that is claimed. If one of skill in the art can readily anticipate the effect of a change in the subject matter to which the claimed invention is directed, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily

anticipate the effect of a change in the subject matter to which the claimed invention is directed, then there is unpredictability in the art. With respect to the present invention, one cannot readily anticipate the identity or location of a particular gene, mutation or polymorphism that is associated with bipolar disorders. While the present inventors have narrowed the region that this linked to bipolar disorder and have set forth the techniques previously known in the art to search for genes and mutations in regions linked to a disorder, such teachings are not sufficient to enable the skilled artisan to identify genes, mutations and polymorphisms within the D18S68-D18S969 region that are associated with a bipolar disorder without undue experimentation.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-5 are indefinite over the recitation of "equivalent regions." This phrase is not clearly defined in the specification and there is no art recognized definition for this phrase. It is not clear as to what would be the structural or functional properties of "equivalent regions." Accordingly, one cannot determine the meets and bounds of the claimed invention.

RESPONSE TO ARGUMENTS:

In the response, Applicants traversed this rejection by arguing that "one of ordinary skill in the art would recognize the art-known meaning of this term as referring

to an equivalent physical location on chromosome 18q or a region that occupies the same genetic locus." Additionally, Applicants filed a 132 Declaration by Christine Van Broeckhoven stating that based on her experience and knowledge, she "would understand the term 'equivalent region' as used in this context as referring to the region of DNA which occupies the same physical location, i.e., the same genetic locus, in the genome of the afflicted individual." The 132 declaration further states that the human genome has been mapped and that using this map one can identify genes that occupy the same physical or genetic locus.

Applicants arguments and the 132 declaration have been fully considered. While the definition set forth in the response and in the declaration include one possible interpretation of this phrase, there is no art recognized definition for this phrase which limits its meaning to that set forth in the response and the declaration. This phrase was not defined in the originally filed application. Further, there is no evidence of record to suggest that those of skill in the art do not view the phrase "equivalent regions" as limited to only regions that have the same physical location. The term "equivalent" means "having similar or identical effects." It is unclear as to what type DNA regions would have similar or identical effects. Thereby, it is unclear as to whether "equivalent regions" include regions which share some degree of sequence identity (99%, 90%, 80%, 50% etc), or regions which contain translocated sequences. If Applicant intends for this phrase to be limited to DNA which occupies the same physical location in the genome or to the same genetic locus, then the claims should be amended to recite such a limitation, to the extent that this limitation is supported by the specification as originally

filed. Accordingly, because the specification does not clearly define what is intended to be encompassed by "equivalent regions" and because there is no art fixed definition for this phrase, it is maintained that the artisan would not be able to determine the meets and bounds of the claimed invention.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (571) 272-0747. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571)-272-0745.

The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866)-217-9197 (toll-free).

Carla Myers
January 4, 2006

CARLA J. MYERS
PRIMARY EXAMINER